Monoclonal Gammopathy of Undetermined Significance (MGUS) and Smoldering Multiple Myeloma (SMM)

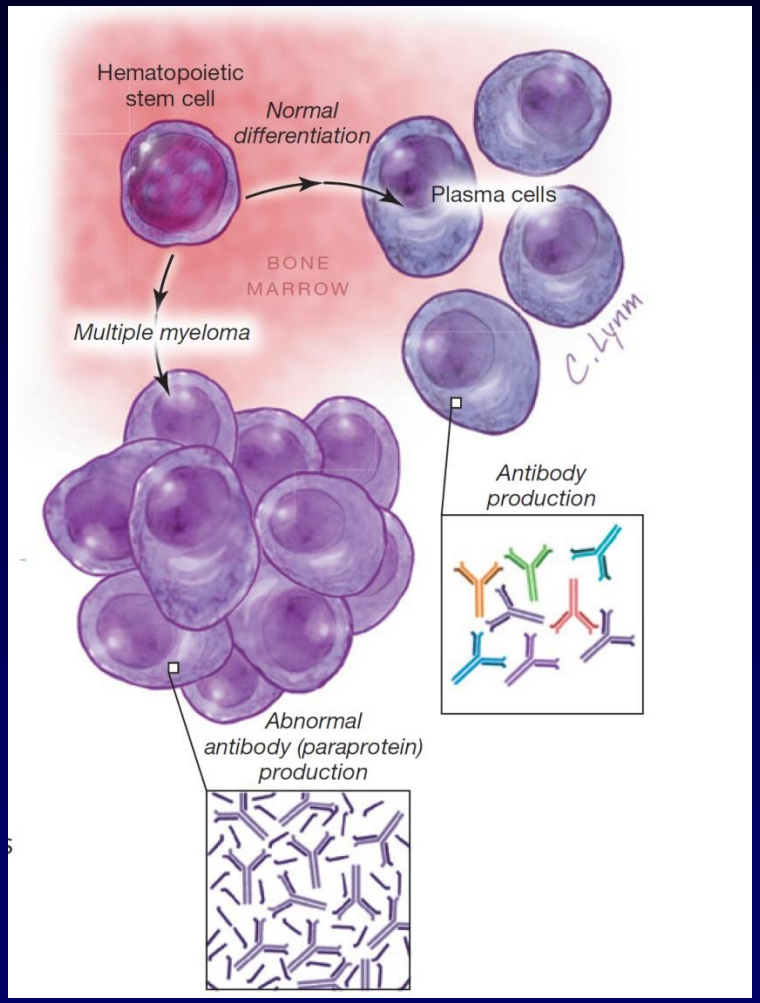
BHS training

08/05/2015

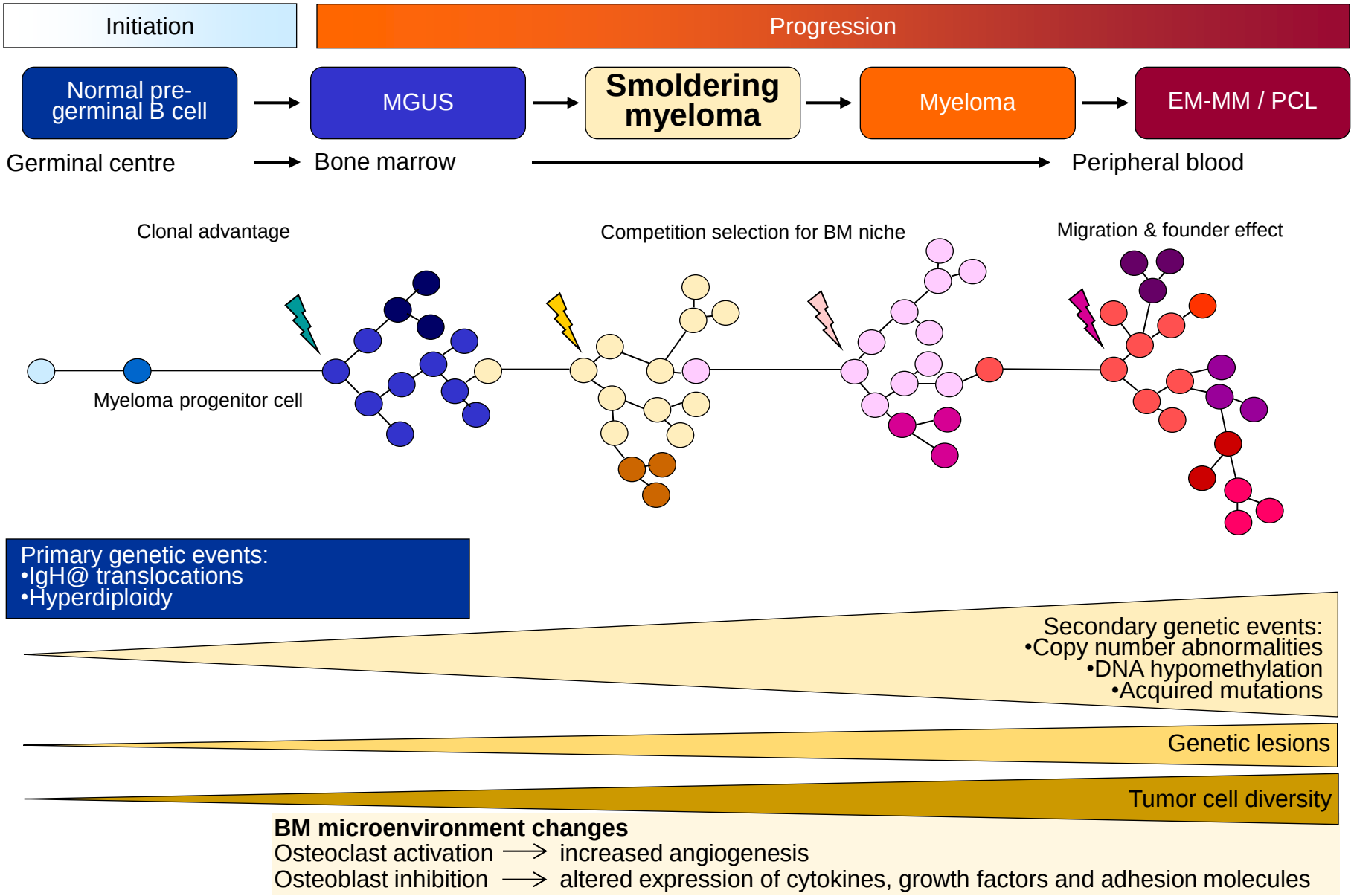
Jo Caers
CHU Liège

Multiple myeloma precursor disease

- Monoclonal gammopathy of undetermined significance (MGUS): 3% of Caucasians (> 50 years)
  - Afro-american
  - Obesity
  - Family members
- Smoldering myeloma (SMM) accounts for approximately 15-34% of all newly diagnosed MM patients



Progression and clonal evolution in Myeloma



Criteria for diagnosis

MGUS

- M spike < 3g/dl
- Clonal BMPC< 10%

AND

Absence of anemia, bone lesions, normal calcium and kidney function

Smoldering MM

- M spike ≥ 3g/dl
- Clonal BMPC ≥ 10%

Active MM

- M spike ≥ 3g/dl
- Clonal BMPC ≥ 10%

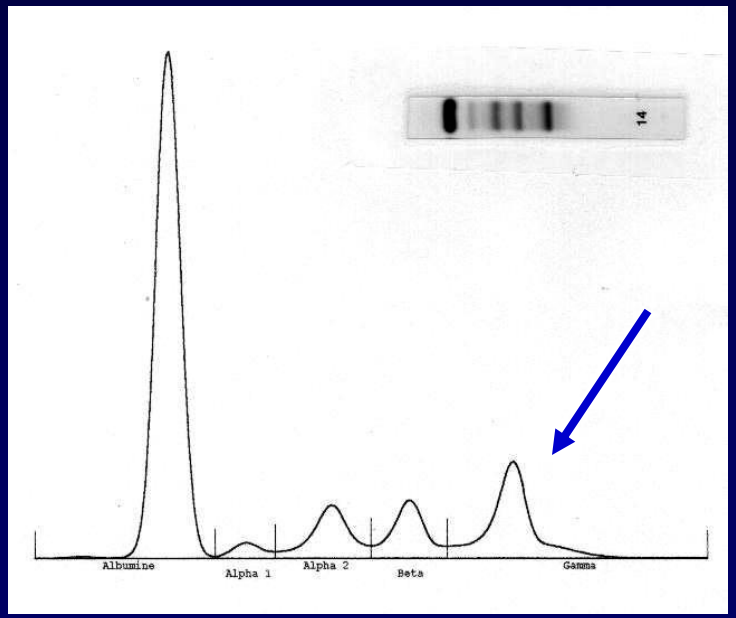
AND

Presence of anemia, bone lesions, high calcium or abnormal kidney function

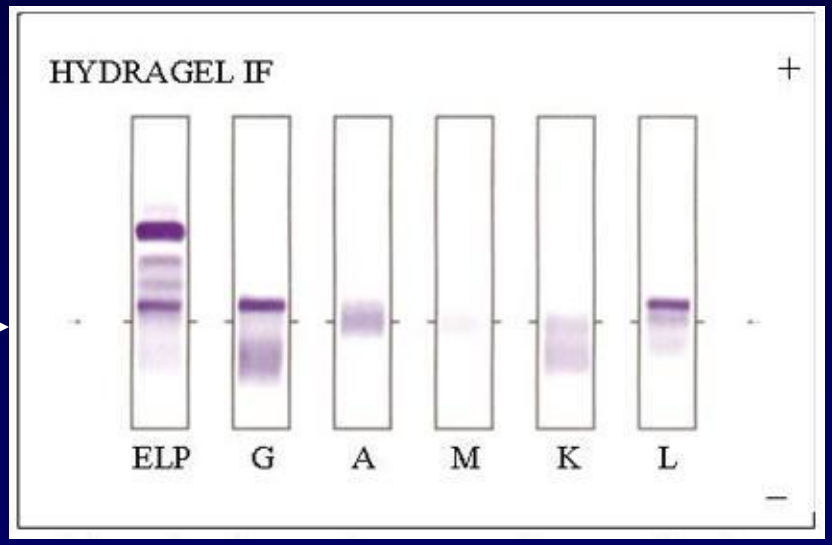
Kyle, IMWG criteria, Leukemia 2010

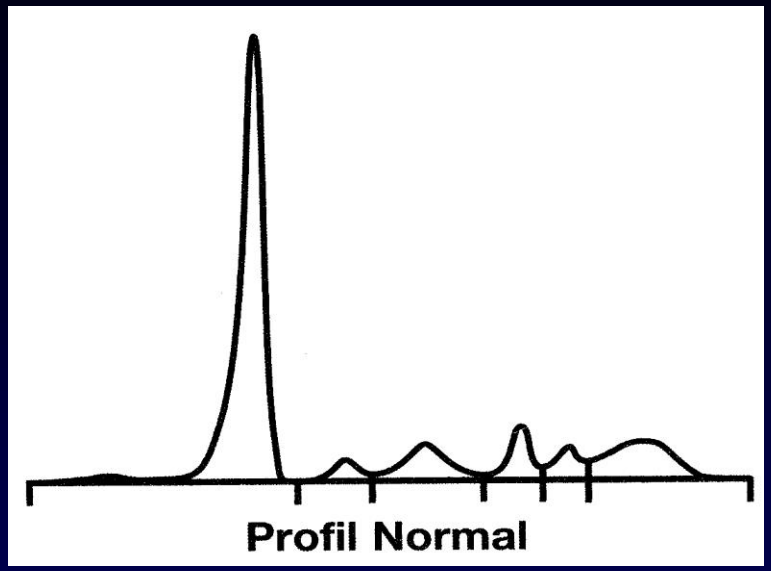
The M Spike

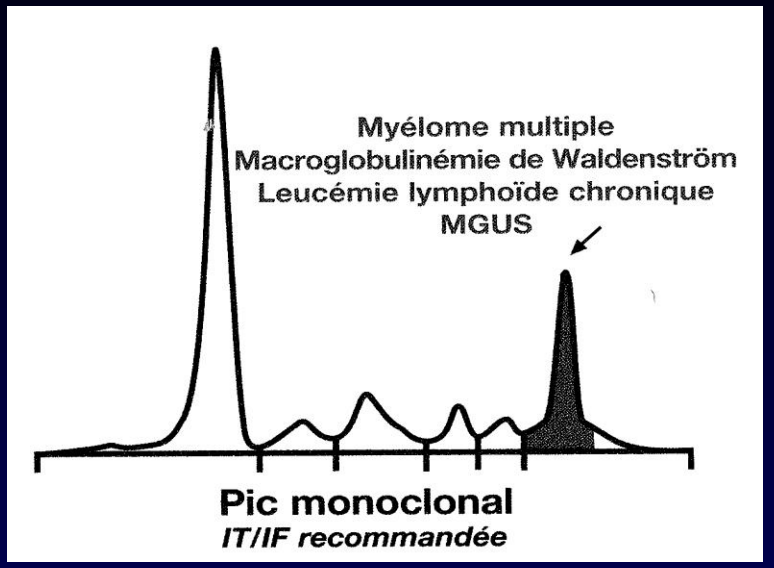
Serum electrophoresis

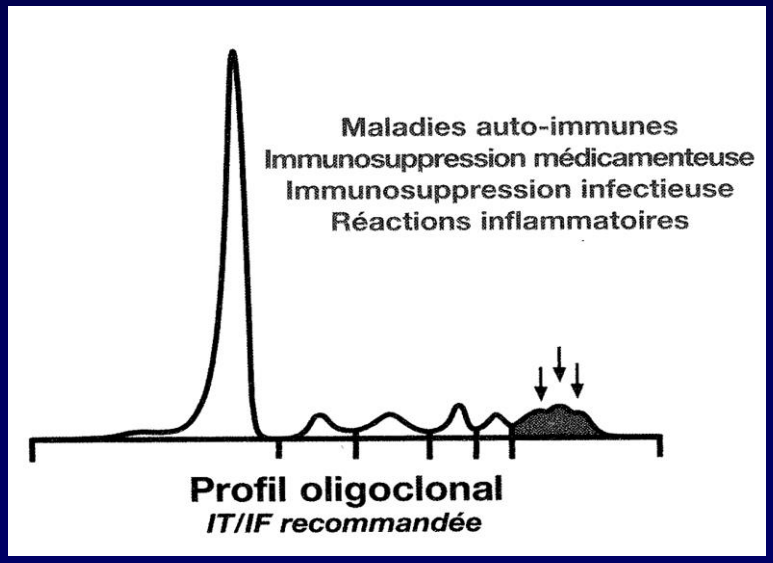


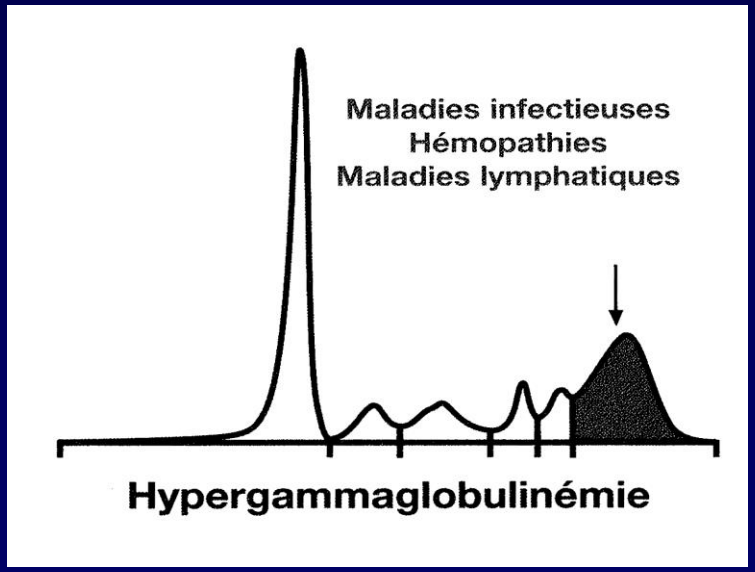
Immunofixation

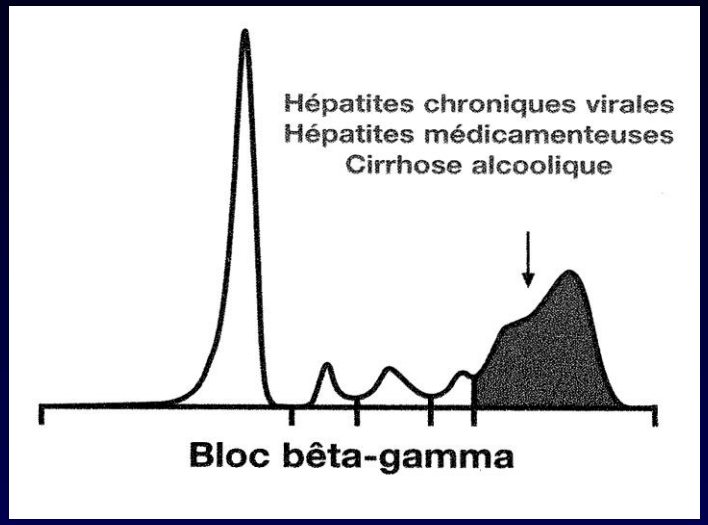


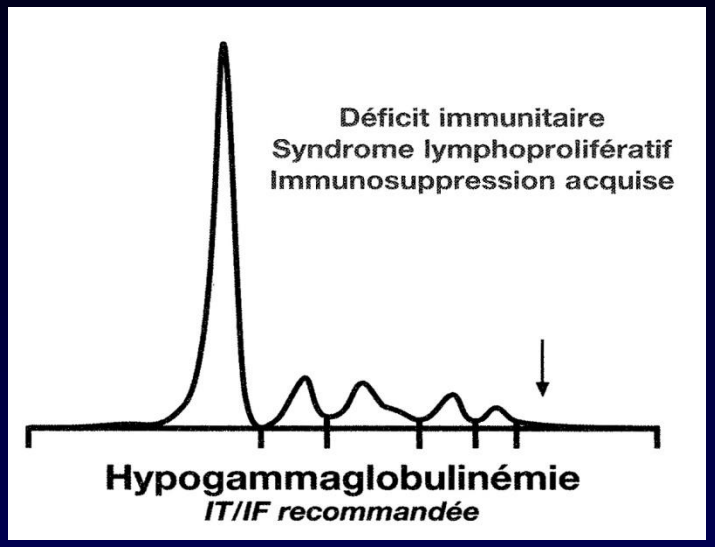

Profil Normal

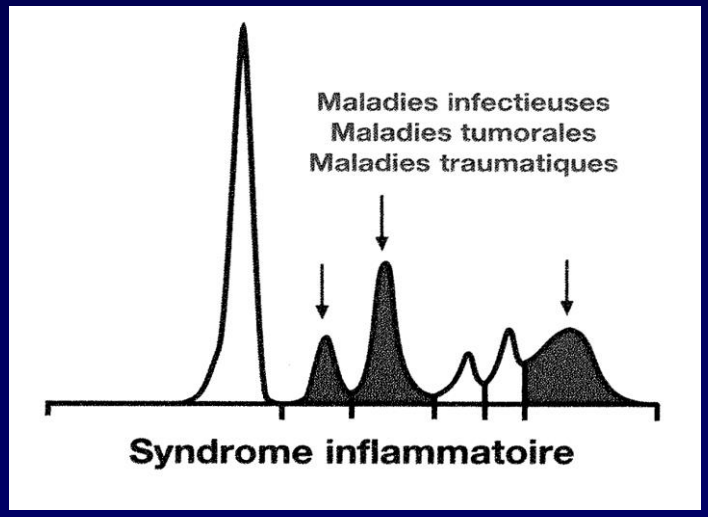

Myélome multiple
Macroglobulinémie de Waldenström
Leucémie lymphoïde chronique
MGUS
Pic monoclonal
IT/IF recommandée

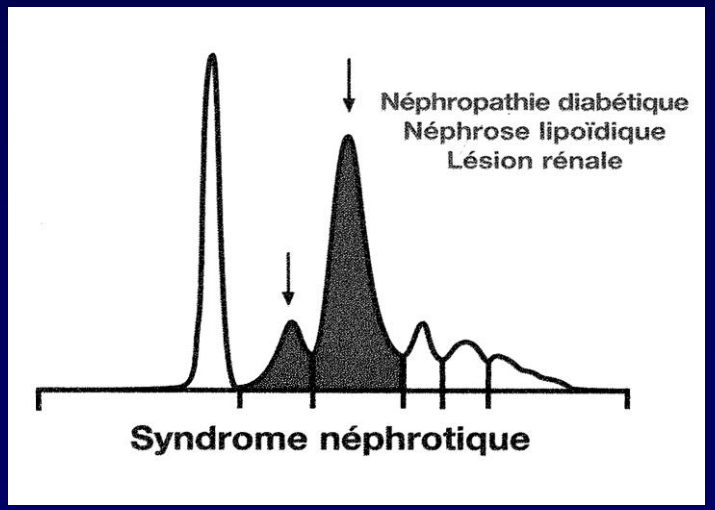

Maladies auto-immunes
Immunosuppression médicamenteuse
Immunosuppression infectieuse
Réactions inflammatoires
Profil oligoclonal
IT/IF recommandée


Maladies infectieuses
Hémopathies
Maladies lymphatiques
Hypergammaglobulinémie


Hépatites chroniques virales
Hépatites médicamenteuses
Cirrhose alcoolique
Bloc bêta-gamma


Déficit immunitaire
Syndrome lymphoprolifératif
Immunosuppression acquise
Hypogammaglobulinémie
IT/IF recommandée


Maladies infectieuses
Maladies tumorales
Maladies traumatiques
Syndrome inflammatoire


Néphropathie diabétique
Néphrose lipoïdique
Lésion rénale
Syndrome néphrotique

Causes of monoclonal gammopathies

Plasma cell disorders
- MGUS
- Multiple myeloma
- Amyloid light chain amyloidosis
- Solitary plasmacytoma
- POEMS syndrome
- Castleman's disease

B-cell lymphoproliferative disorders
- Non-Hodgkin's lymphoma
- Chronic lymphocytic leukemia
- Waldenström's macroglobulinemia
- Post-transplant monoclonal gammopathies

Infections
- Bacterial
- Viral (hepatitis, EBV, CMV, HIV)

Autoimmune disorders
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Sjögren syndrome
- Scleroderma
- Psoriatic arthritis

Skin disorders

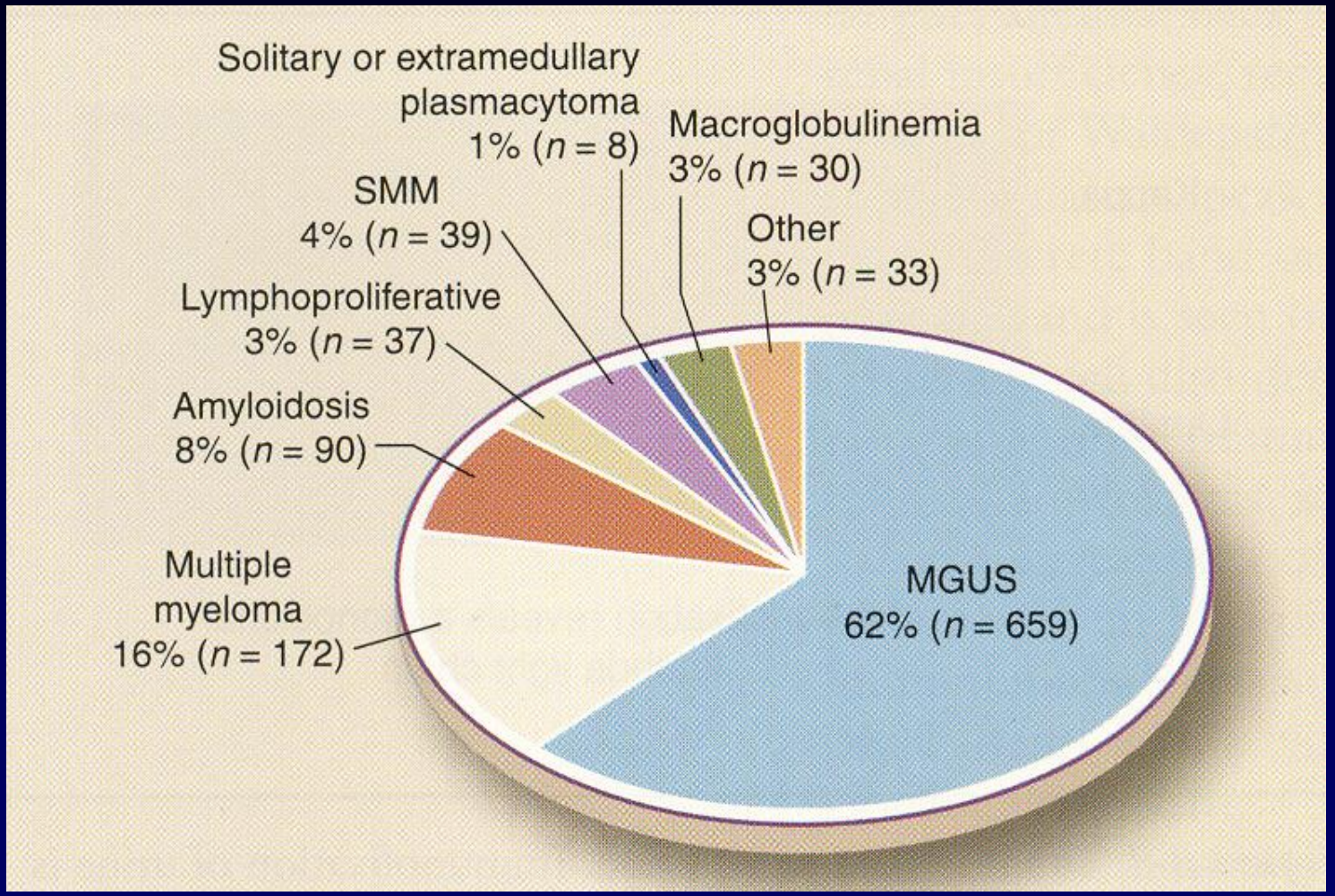
Liver disorders

Glomerular nephropathies

Epithelial cancers
(paraneoplastic syndromes)

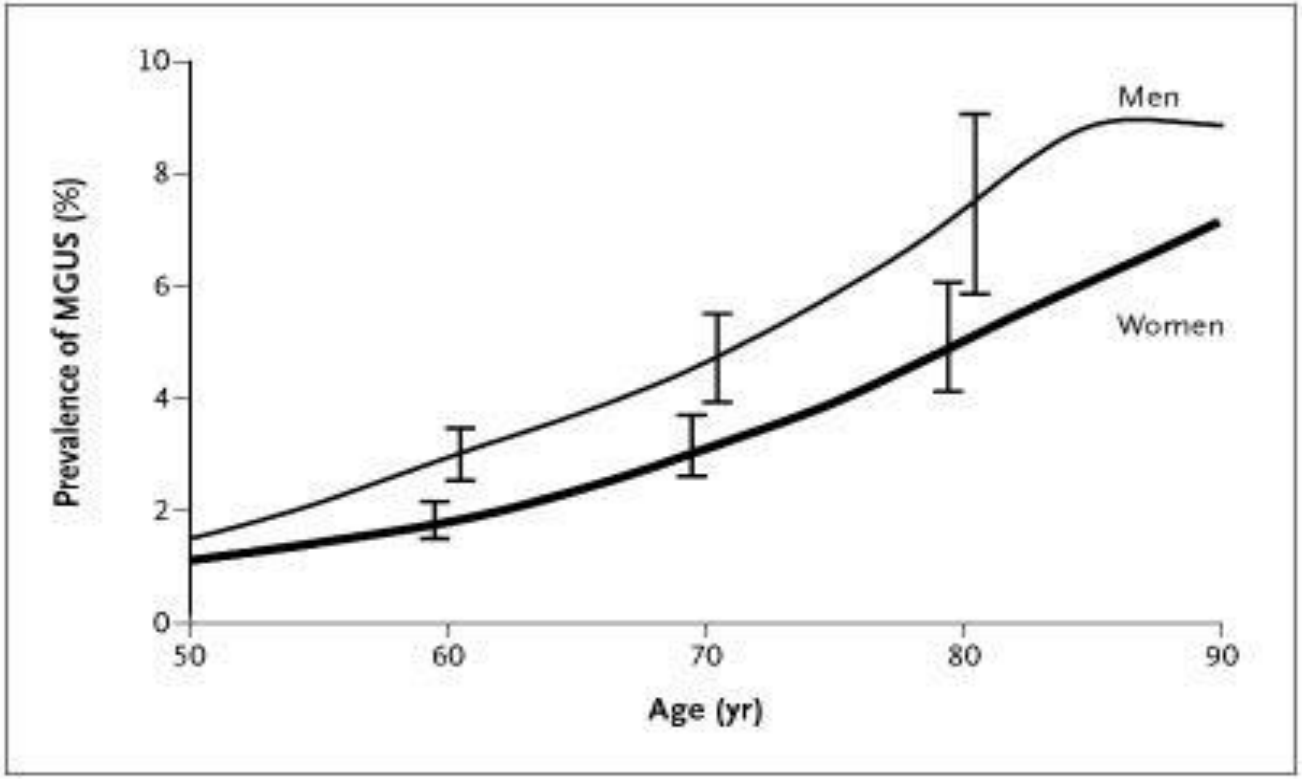
Other hematological disorders
- Cryoglobulinaemia
- Myelodysplastic or myeloproliferative disorders
- Coagulation disorders

Caers J et al Ann Med 2013

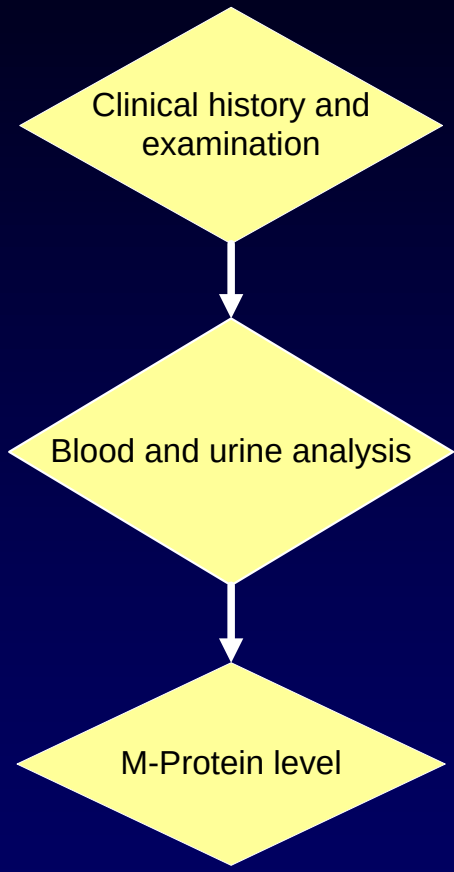


Kyle, Mayo Clin Proc 1998

Incidence of MGUS



Advancing in the diagnosis

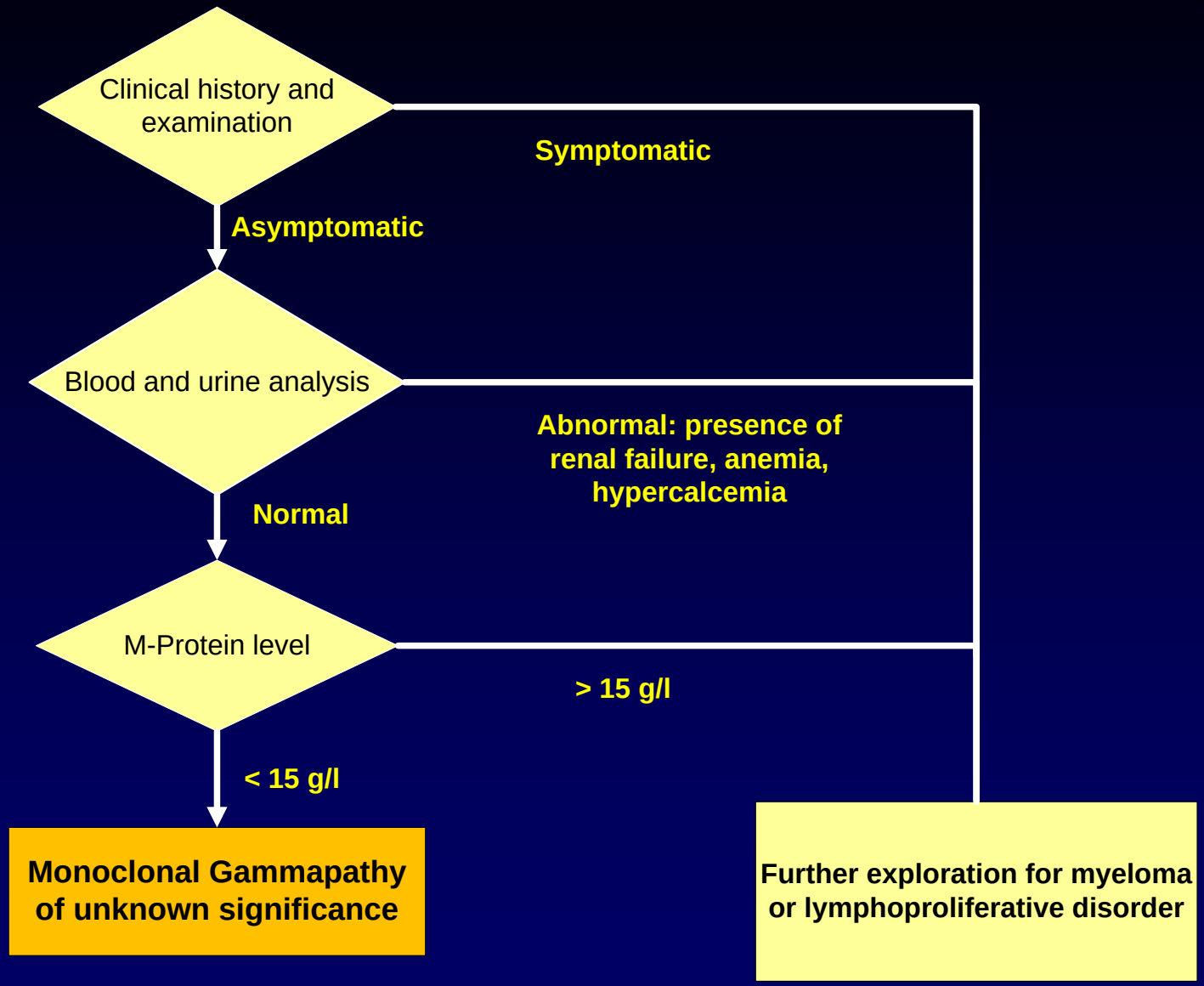


Caers J et al Ann Med 2013

Alerting symptoms

Signs and symptoms	Diagnostic findings	Pathogenic mechanisms
Bone/back pain, cord compression, cauda equina	Lytic lesions, pathologic fractures, severe osteopenia	Myelophthisis, increased osteoclastogenesis, osteoblast inhibition, solitary plasmacytoma
Fatigue, malaise	Anemia	Myelophthisis, decreased EPO, hemolysis
	Renal Failure	Light chain deposition, cast nephropathy, hypercalcemia-induced vasoconstriction, amyloidosis, urate nephropathy
	Hypercalcemia	Bone reabsorption secondary to myelophthisis and cytokine release
	Hepatitis, liver failure	Amyloid infiltration, MM cell infiltration
Recurrent infections	Hypogammaglobulinemia, leukopenias	Myelophthisis
Neurologic symptoms	Polyradiculopathy, ischemic strokes, altered mental status	Amyloid deposition, cryoglobulinemia type I, hyperviscosity, hypercalcemia, uremia
Respiratory distress	Infiltrative cardiomyopathy, arrhythmias, pleural effusions, pulmonary edema	Cardiac or pulmonary amyloid, plasmacytoma, malignant pleural effusions, hyperviscosity
Purpura, petechiae, bleeding, acrocyanosis	Cryoglobulinemia type I, thrombocytopenia, hyperviscosity	M spike deposition, myelophthisis, hyperviscosity

Bianchi G, Hematol Oncol Clin North Am. 2012



Caers J et al Ann Med 2013

Further exploration for myeloma or lymphoproliferative disorder

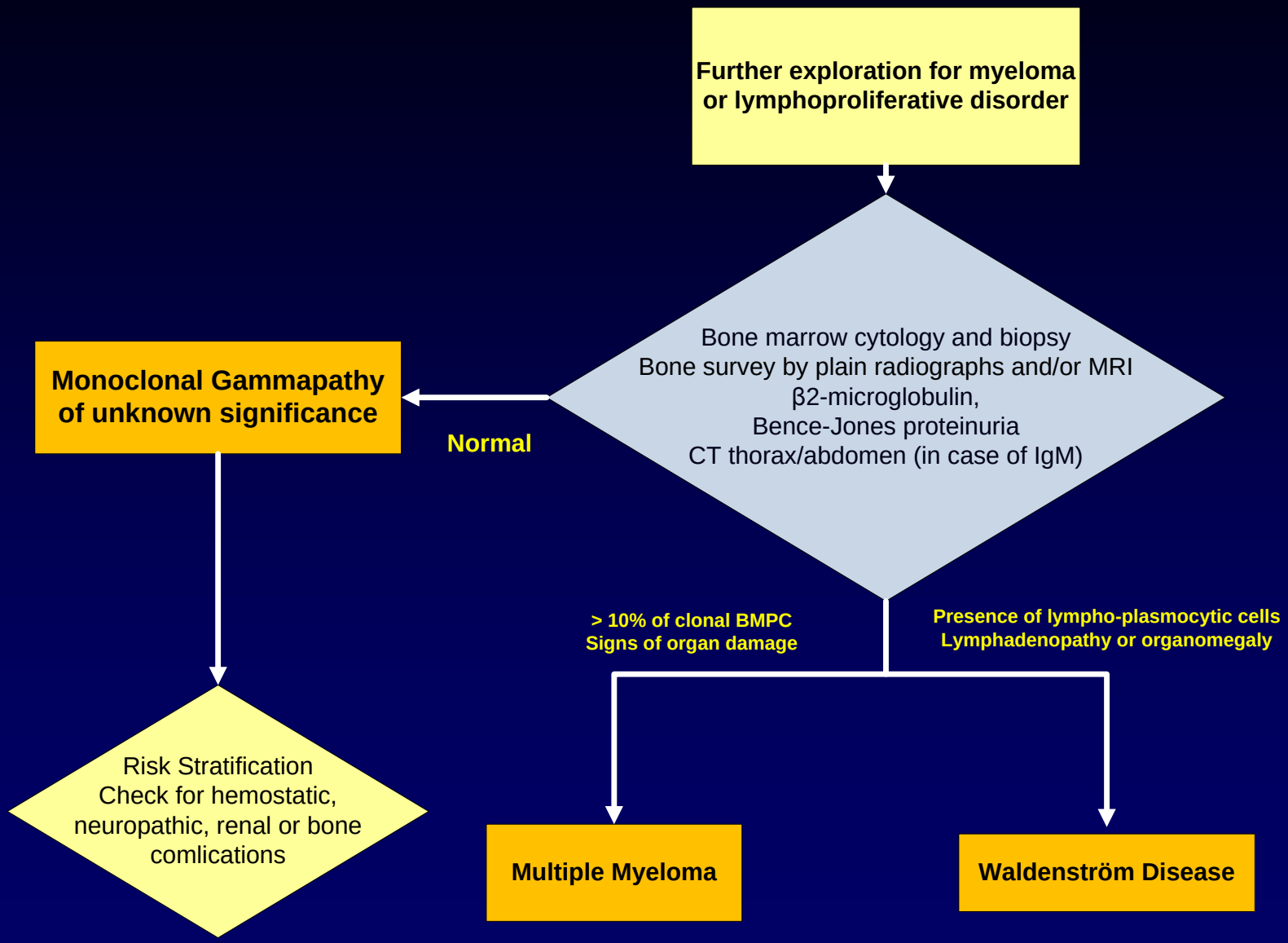
Ig M

BM cytology/biopsy

CT scan thorax/abdomen

IgG, IgA, κ or λ

BM cytology/biopsy
Bone Survey
Blood and urine testing
Cytogenetics



Caers J Ann Med 2013

Risk stratification

- Level of M-protein 1.5 g/dl
- Isotype IgG vs IgA, IgM
- BM plasmocytosis 5%
- Reduced Ig levels
- Serum Free Light Chain ratio

Kyle, NEJM, 2002
Rosinol, Mayo Clin Proc, 2007

Risk Stratification for MGUS

Mayo Clinic (n= 1148)

No of risk factors	No of patients, n(%)	Progression at 20 years
0	449 (38)	5%
1	420 (37)	21%
2	226 (20)	37%
3	53 (5)	58%

Risk Factors

- **non IgG MGUS**
- **M protein > 1.5 g/dl**
- **FLC ratio < 0.26 or > 1.65**

Rajkumar, Blood, 2005

PETHEMA (n= 276)

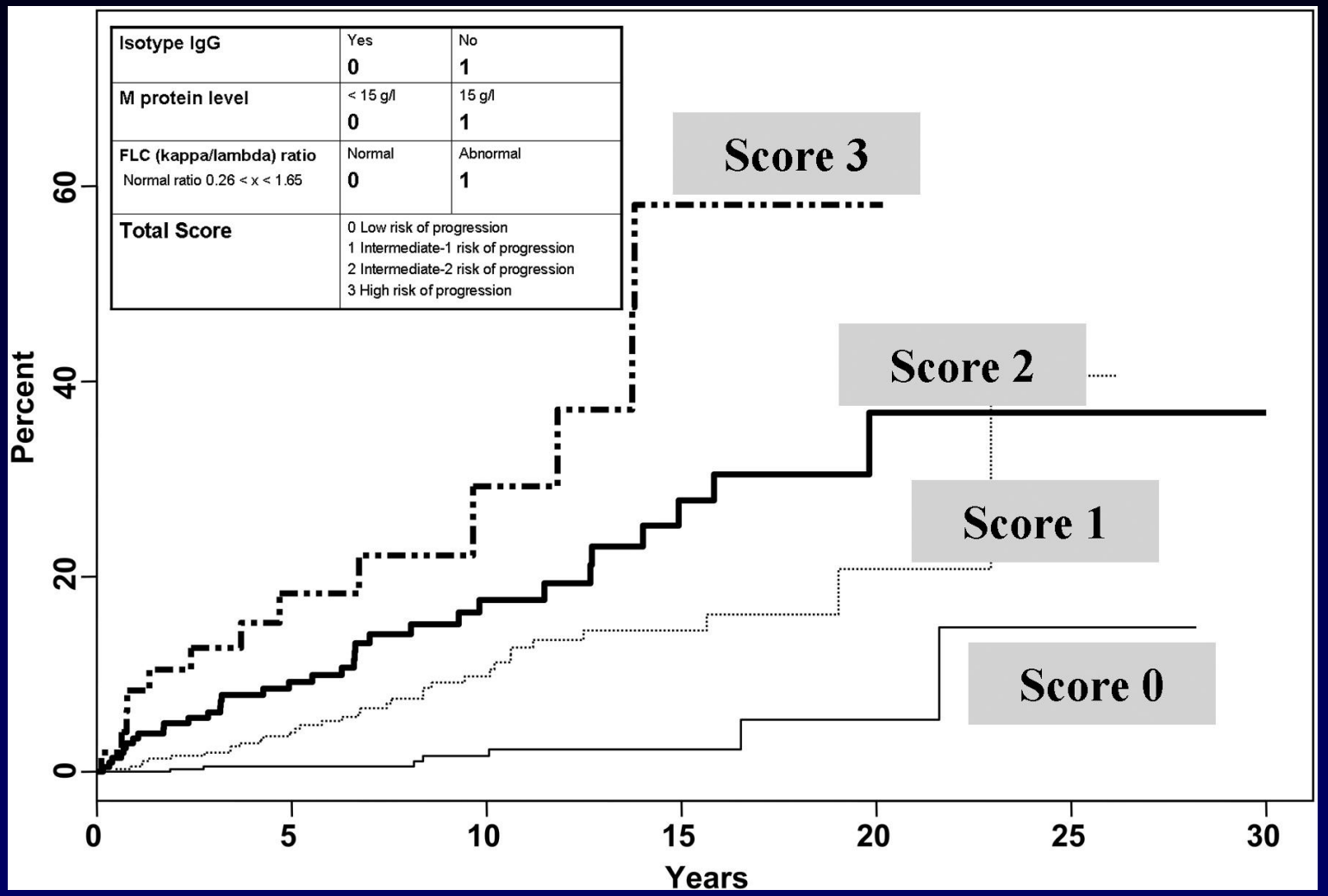
No of risk factors	No of patients, n(%)	Progression at 5 years
0	127 (46)	2%
1	133 (48)	10%
2	16 (6)	46%

Risk Factors

- **> 95% of abnormal BMPC ***
- **DNA aneuploidy**

* Decreased CD38 expression, expression of CD56, absence of CD19 and/or CD45

Perez-Persona, Blood, 2007



Caers, Ann Med 2013
Rajkumar, Blood, 2005

Current IMWG recommendation

- **Low-risk MGUS**
  - Baseline BM cytology and skeletal survey not routinely indicated
  - Serum electrophoresis in 6 months and if stable, follow either every 2 years or if symptoms arise

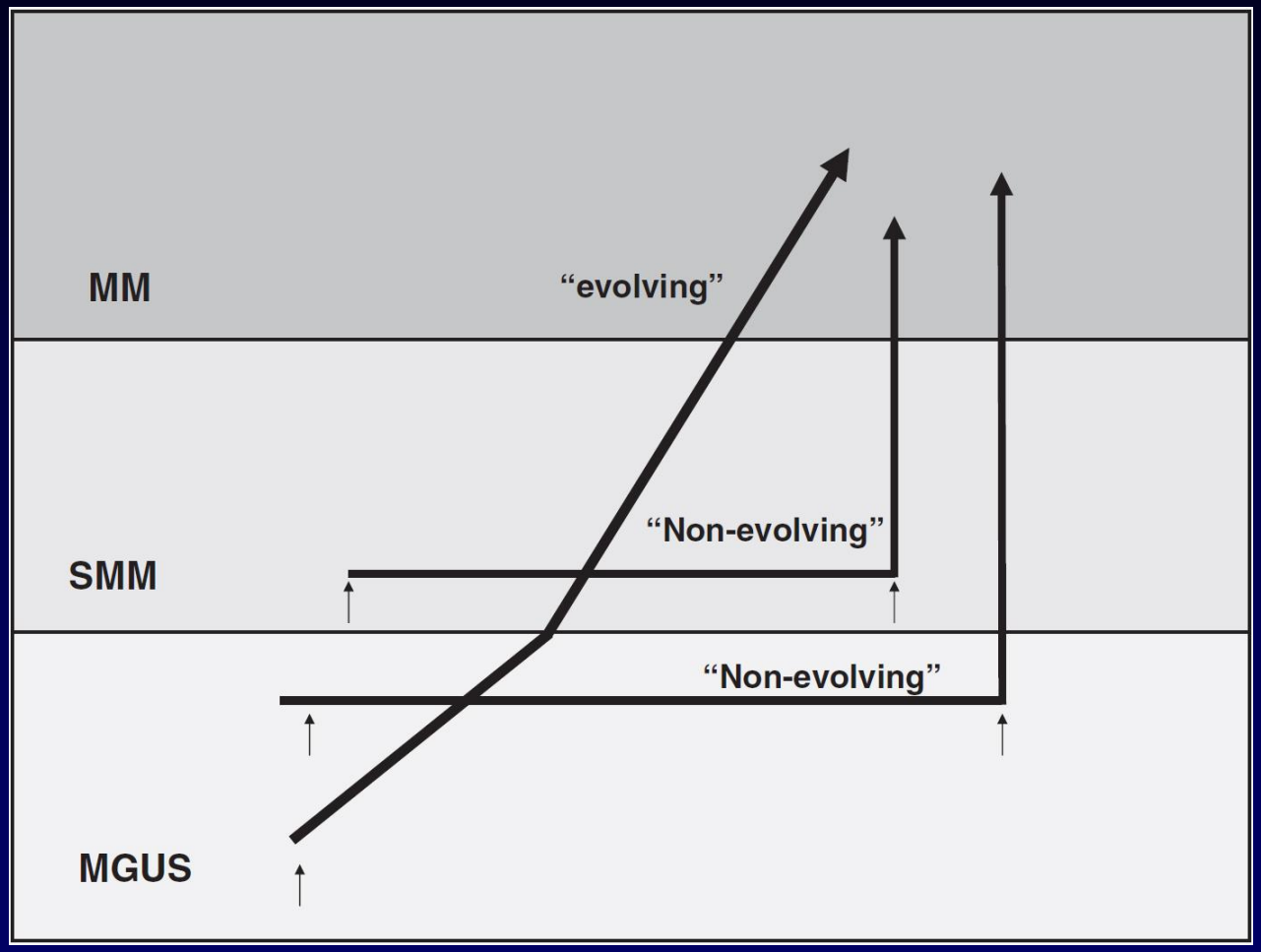
- **Intermediate and high-risk MGUS**
  - Baseline BM cytology/biopsy and skeletal survey
  - Blood analysis (including serum electrophoresis) repeated in 6 months and than annually

Kyle, IMWG criteria, Leukemia 2010

Every MM is preceded by an MGUS

Years prior to MM	M-spike	Abnormal FLC ratio	MGUS
2	25/27	23/27	27/27
3	54/58	46/58	57/58
4	45/48	29/46	47/48
5	34/37	25/37	35/37
6	25/25	19/25	25/25
7	14/15	11/15	14/15
8 or more	13/17	8/17	14/17

Landgren, Blood 2009



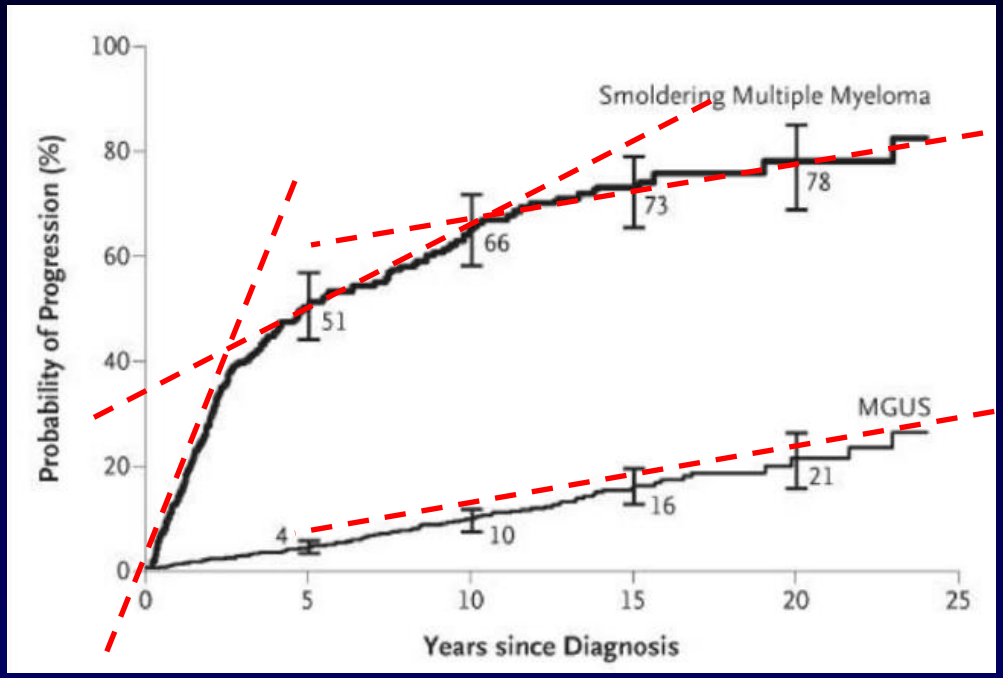
Blade, Leukemia, 2008

MGUS, not that benign

- Increased risk of fractures
- Decreased bone densities
- Increased risk for venous and arterial thrombosis
- Neuropathy
  - IgM anti-MAG neuropathie
  - IgA, IgA CIPD
- Increased risk of infections

Smoldering Multiple Myeloma

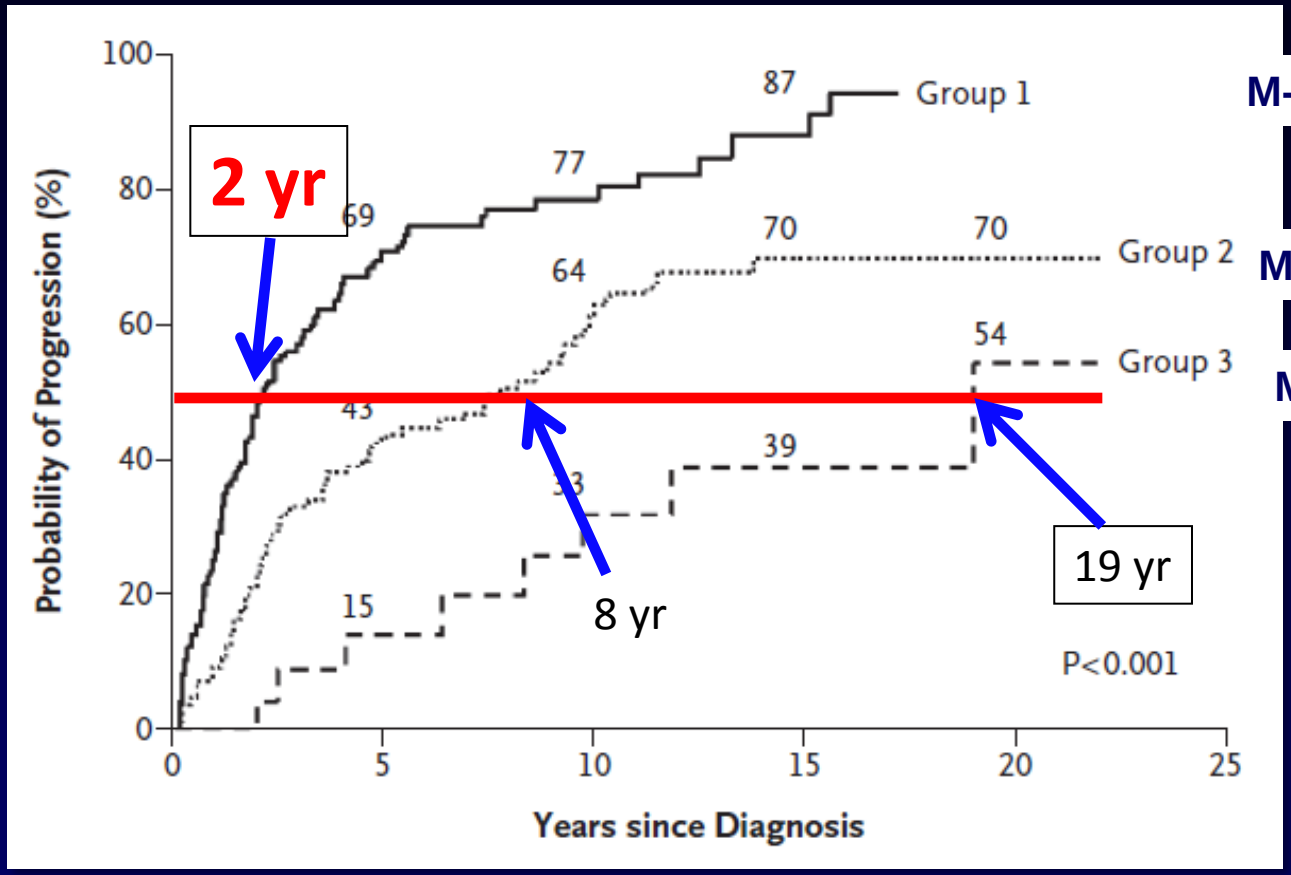
Smoldering MM



- 276 SMM patients diagnosed 1970-1995
- 163 (59%) progressed
  - 158 MM
  - 5 amyloidosis
- Overall risk of progression (per year)
  - 10% in the first 5 years
  - 3% in the next 5 years
  - 1% in the next 5 years

Kyle, NEJM, 2007

Heterogenous entity

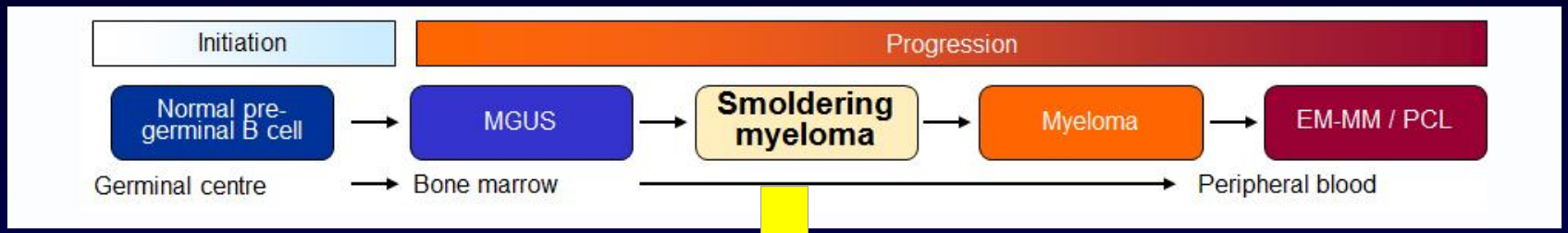


M-Protein > 30 g/l, PC > 10%

M-Protein < 30 g/l, PC > 10%

M-Protein > 30 g/l, PC< 10%

Kyle R *et al.* N Engl J Med 2007;356:2582-2590



Is it possible to identify high-risk patients?

Has an early treatment an additive value?

Smoldering myeloma

Cure ?

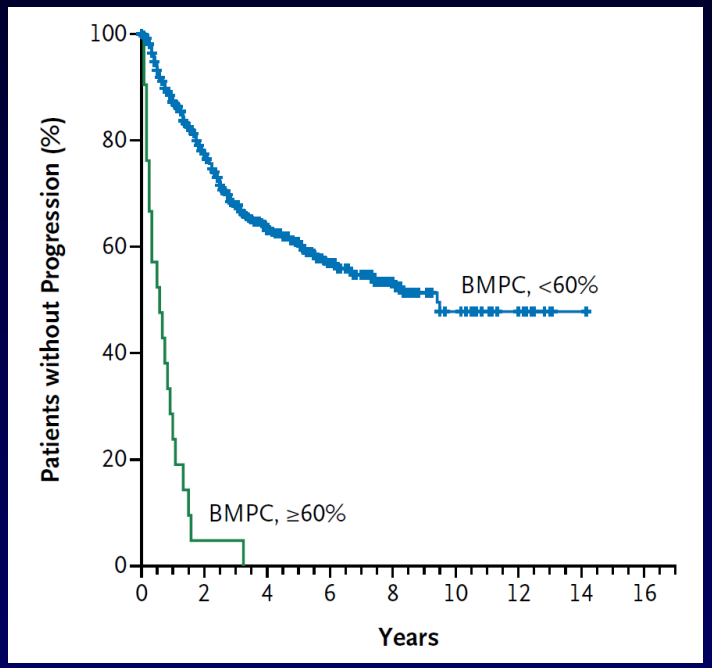
Select an agressive clone ?

Delay progression?

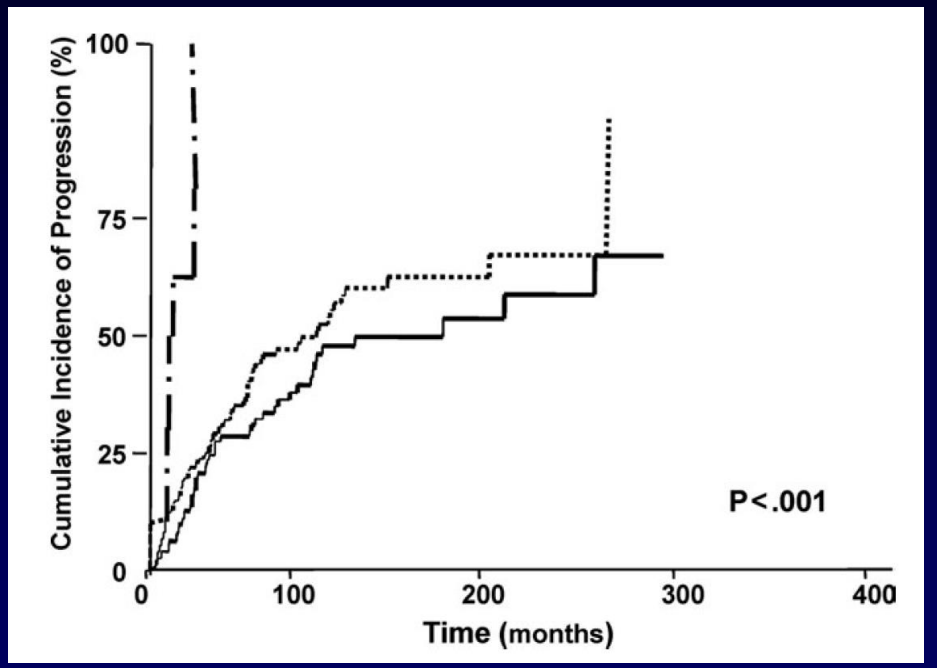
Limit complications ? (bone disease, renal failure)

Ultra-high risk (> 80%)
Bone marrow plasmocytosis > 60%
Serum free light chain ratio > 100
> 1 focal lesion on axial MRI

Bone Marrow: plasmocytosis

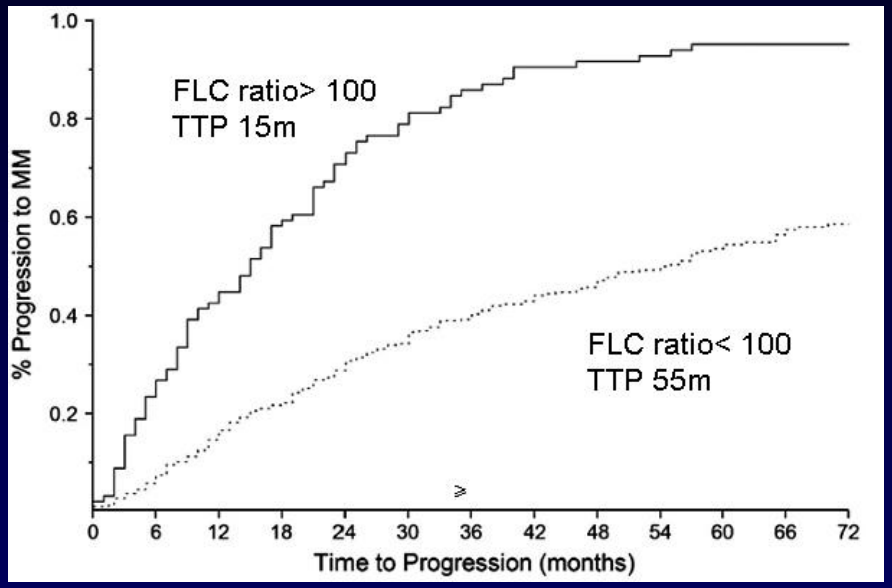


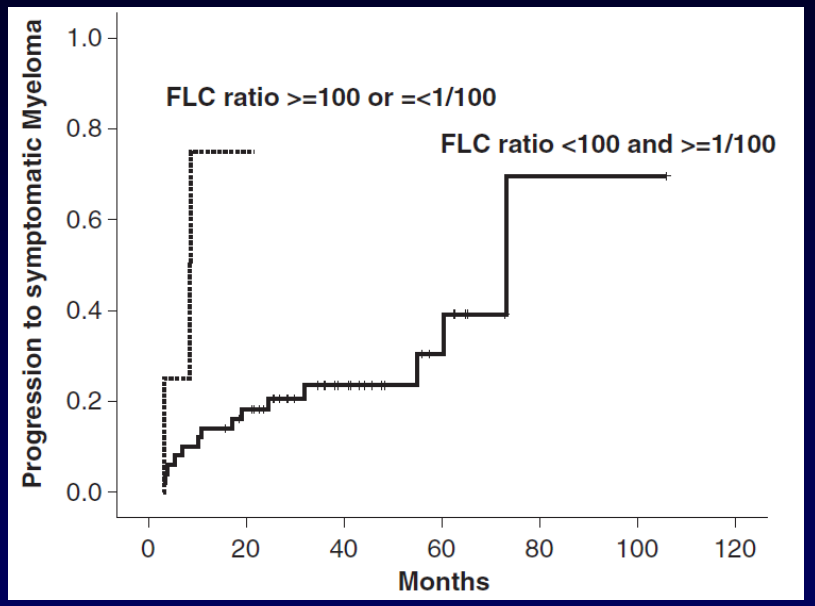
Rajkumar, NEJM, 2011



Rago, Cancer, 2012

Serum: FLC > 100





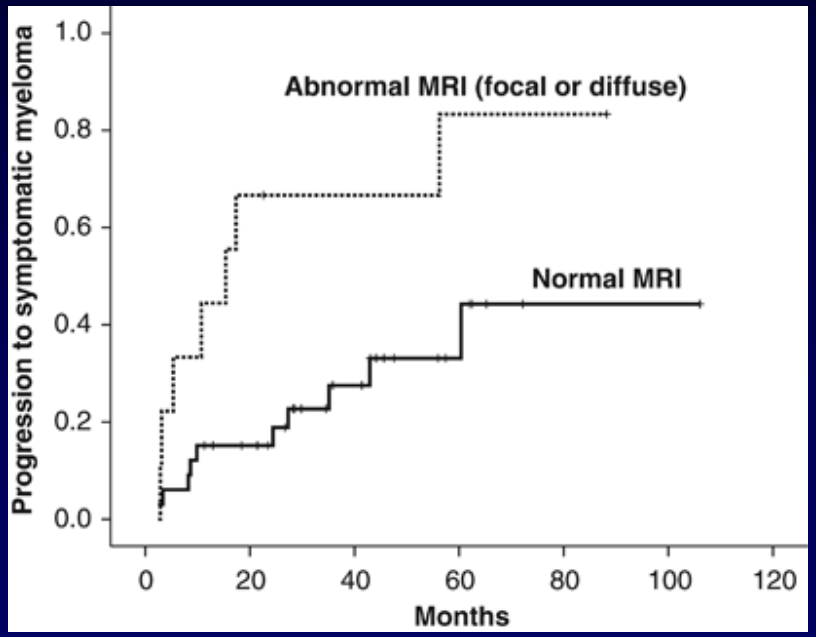
Prognostic variable	*Hazard ratio*
BMPC, %	3.24
Serum M-spike	3.16
FLC ratio > 100	3.23

Larsen, Leukemia 2013

Kastritis, Leukemia 2012

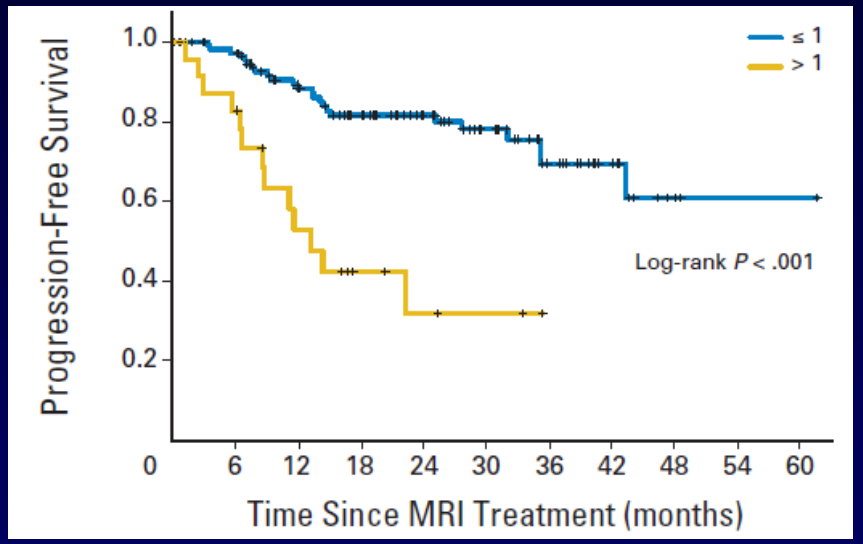
MRI

Axial MRI (n 96)



Kastritis, Leukemia, 2013

Whole body MRI (n 147)



Hillengass, JCO, 2010

Diagnosis of MM requires the presence of a clonal bone marrow plasmocytosis ≥10% or biopsy proven plasmacytoma and 1 or more of the following criteria

- **Evidence of end organ damage, attributable to the underlying plasma cell proliferative disorder**
  - Hypercalcemia
  - Renal insufficiency
  - Anemia
  - Bone lesions
- **Biomarkers of malignancy**
  - Clonal bone marrow plasma cells ≥60%
  - Involved/uninvolved serum free light chain ratio ≥100
  - >1 focal lesions on magnetic resonance imaging studies

Rajkumar, Lancet Oncology, 2014

High risk
MAYO CRITERIA (PC, M-protein, FLC)
PETHEMA CRITERIA (Flow cytometry and immunoparesis)
Increase in paraprotein during follow-up
Diffuse bone marrow infiltration on MRI
Presence of circulating plasma cells
High-risk cytogenetics (del 17p, t(4;14), +1q21)

Risk Stratification for SMM

Mayo Clinic (n= 273)

No of risk factors	No of patients, n(%)	Progression at 5 years
1	76 (25)	25%
2	115 (42)	51%
3	82 (30)	76%

Risk Factors

- **BMPC > 10%**
- **M protein > 3 g/dl**
- **FLC ratio < 0.126 or > 8**

Dispenzieri, Blood, 2008

PETHAMA (n= 89)

No of risk factors	No of patients, n(%)	Progression at 5 years
0	28 (31)	4%
1	22 (25)	46%
2	39 (44)	72%

Risk Factors

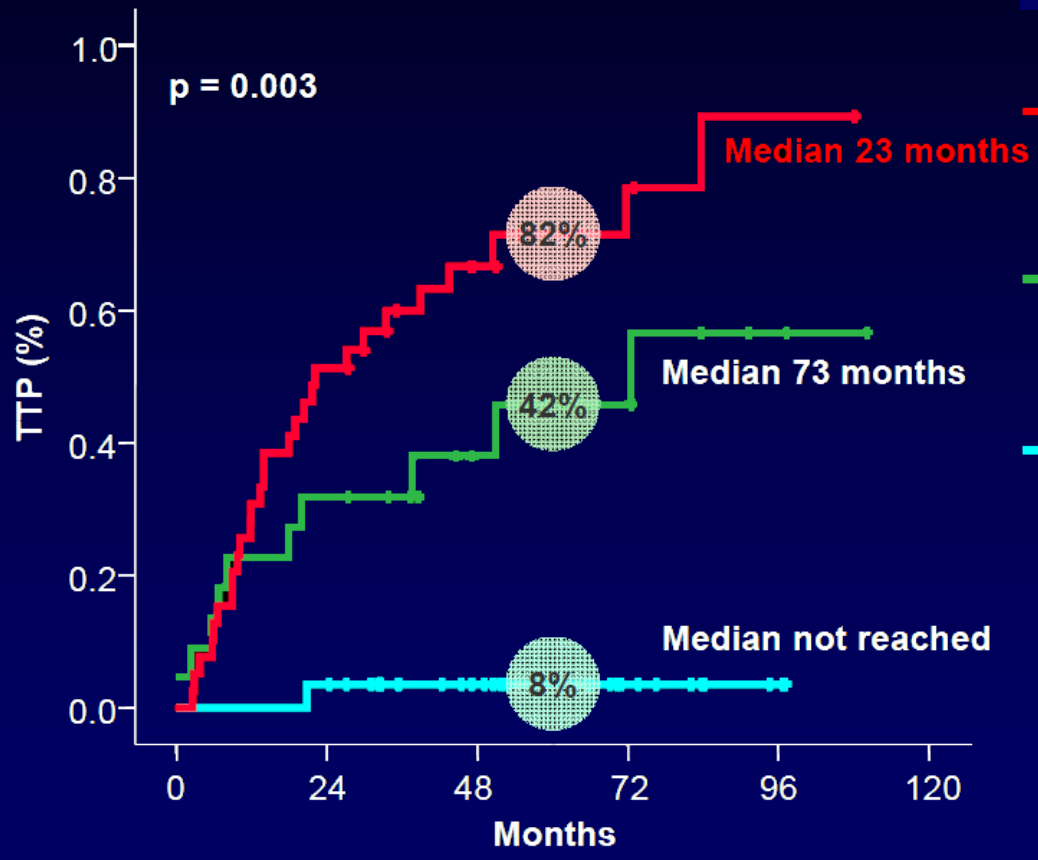
- **> 95% of abnormal BMPC ***
- **Immunoparesis**

* Decreased CD38 expression, expression of CD56, absence of CD19 and/or CD45

Perez-Persona, Blood, 2007

PETHEMA

- > 95% of abnormal BMPC *
- Immunoparesis



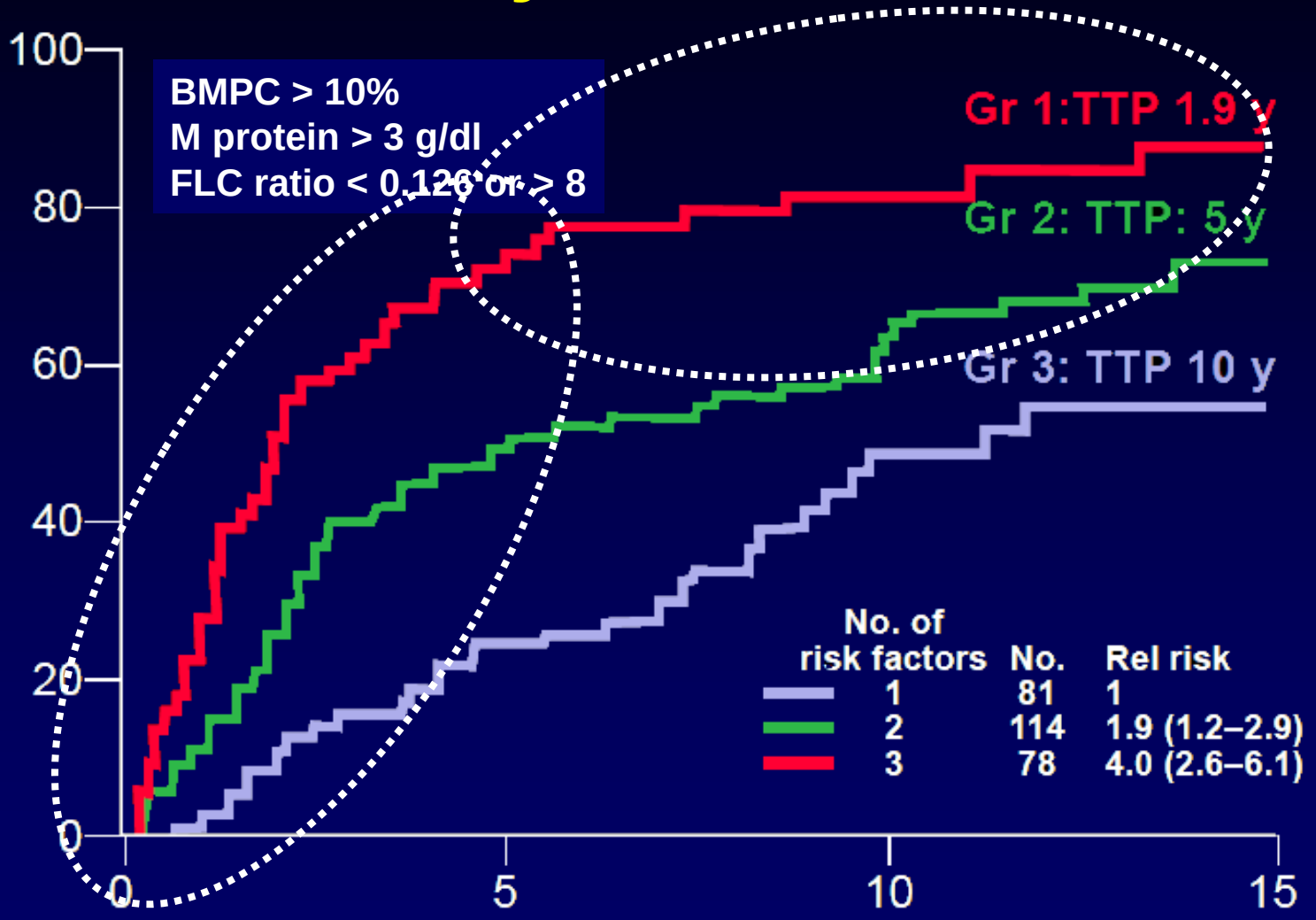
>95% aPC/BMPC + paresis
n = 39 (28 progr.)

> 95% aPC/BMPC or paresis
n = 22 (10 progr.)

No adverse factors
n = 28 (1 progr.)

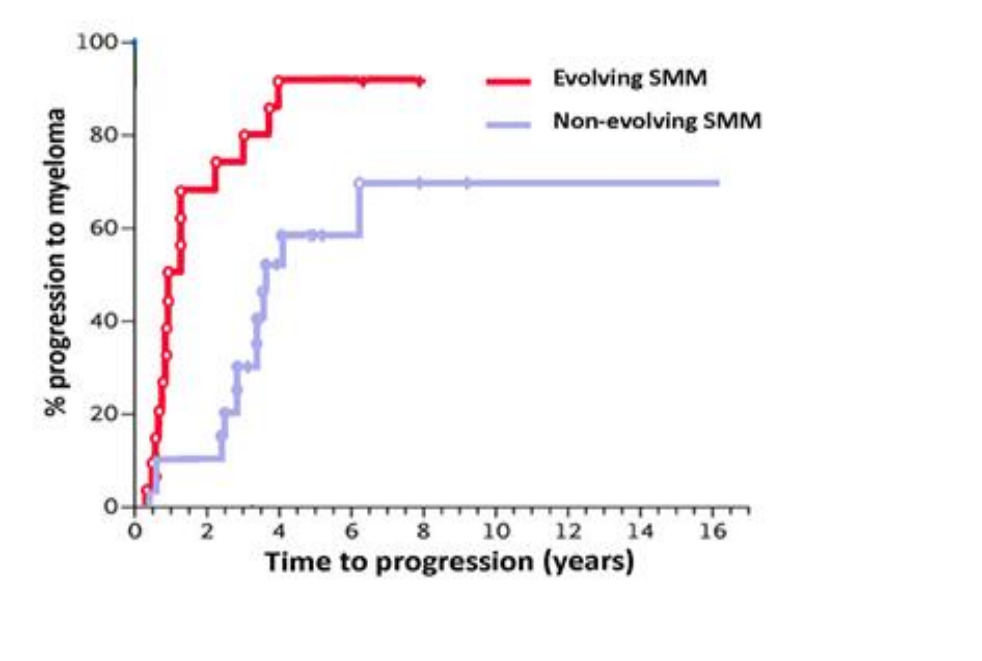
Perez-Persona, Blood, 2007

Mayo Clinic Model



Dispenzieri, Blood, 2008

Progressive M-Component



Increase ≥ 10% in the M-protein level in each of the first two consecutive follow-up visits.

Rosinol, BJH 2003

Cytogenetics

N = 290

Variable	HR	P	Median TTP (years)	TTP rate % at 3 Years
Chromosomal aberrations				
del(17p13)	2.9	0.001	2.04 vs 5.62	56 vs 30
t(4;14)	2.2	0.003	2.91 vs 5.71	55 vs 28
+1q21	1.66	0.02	3.86 vs NA	43 vs 27
high risk		0.001	3.79 vs NA	45 vs 24
Hyperdiploidy	1.67	0.016	3.92 vs NA	35 vs 29
High tumor mass	4.27	< .001	1.23 vs 9.03	67 vs 23
Bone marrow plasma cells (%)				
≥ 10	0.8	0.67	5.62	
≥ 20	2	0.001	3.93	41
≥ 60	4.74	0.018	0.62	N/A
Abnormal sFLC	11.23	0.001	2.7 vs NA	50 vs 8
Aberrant plasma cells 95%	4.37	**< .001**	1.23 vs 9.03	67 vs 23

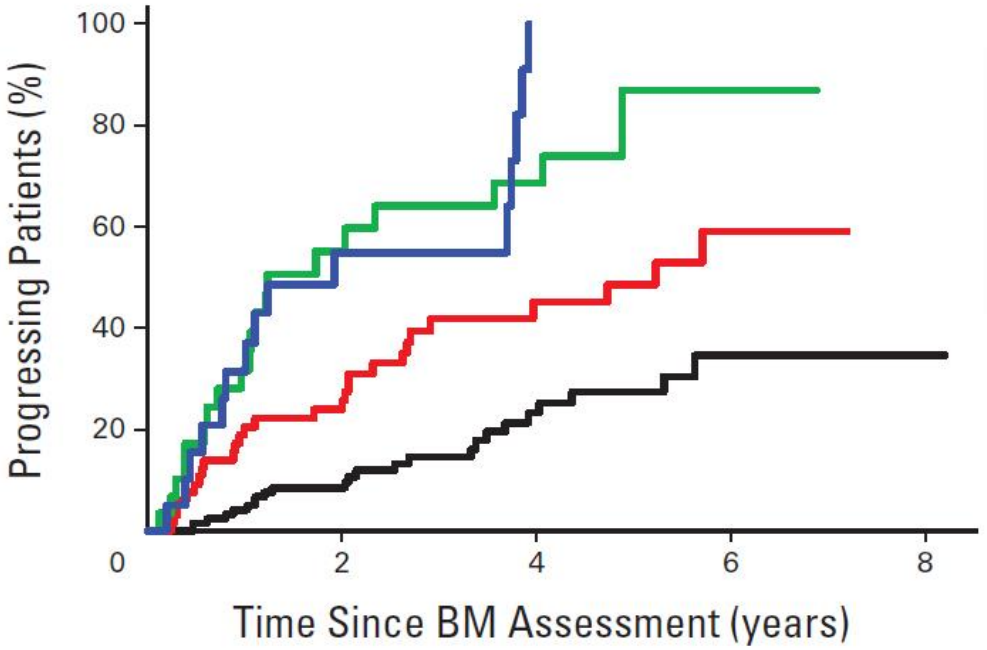
Neben, JCO 2014

Cytogenetics

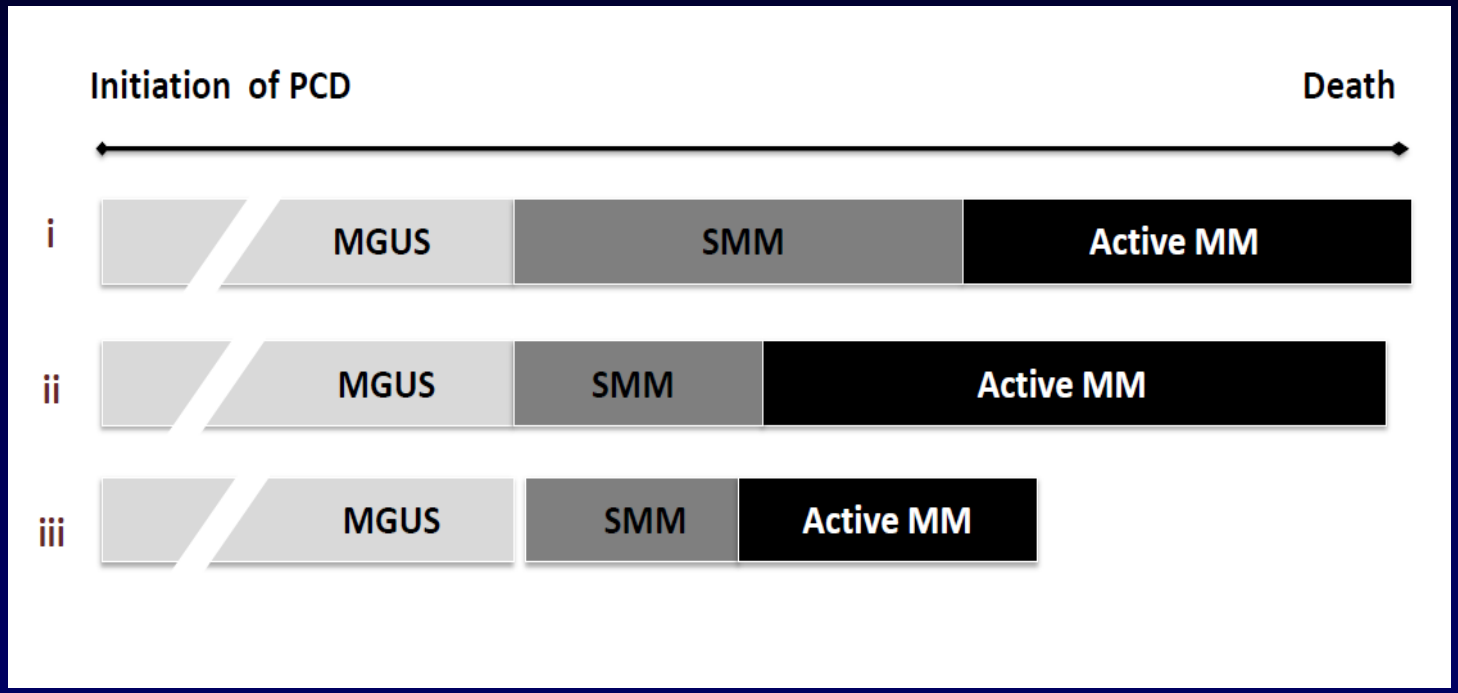
N = 290

Table 2. N

Variable	n	TTP rate at 3 years (%)	HR (95% CI)	P	P*
T mass low, CA risk low	128	15	1 (1.0 to 1.0)	—	< .001
T mass low, CA risk high	67	42	2.26 (1.16 to 4.40)	.016	
T mass high, CA risk low	29	64	4.13 (2.26 to 7.54)	< .001	.53
T mass high, CA risk high	21	55	6.97 (3.98 to 12.22)	< .001	
Aberrant pl					
> 95% v					
Cytogenetic					
High v lo					
Ploidy statu					
Hyperdip					
Tumor mas					
High v lo					
ISS stage					
II/III v I					
Immunopar					
1/2 v 0					



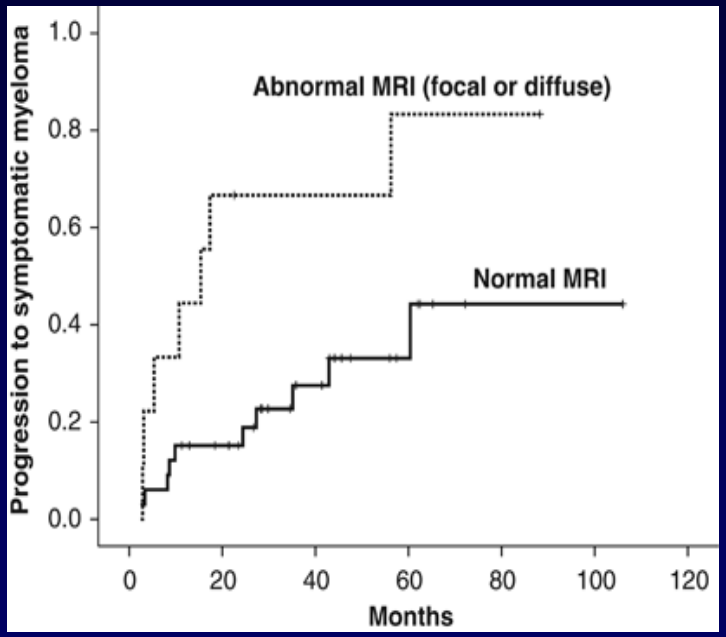
Cytogenetics



Dispenzieri, Blood 2013

Diffuse MRI pattern

Axial MRI (n 96)



Kastritis, Leukemia, 2013

Whole body MRI (n 96)

Table 3. Results of the Multivariate Analysis of All Variables and of Selected Variables for Progression-Free Survival

Variable by Multivariate Analysis Type	Hazard Ratio	*P*
Full model		
MRI-FL above cutoff point of one FL	3.01	.002
Diffuse bone marrow infiltration in MRI	2.37	.03
M protein concentration ≥ 40 g/L	1.87	.44
Presence of IgA	0.84	.71
Reduction of uninvolved Ig	1.03	.95
Presence of urinary Bence Jones protein	0.94	.87
Plasma cell infiltration in bone marrow ≥ 20%	1.30	.53
Final model after backward selection		
MRI-FL cutoff point	3.25	< .001
Diffuse bone marrow infiltration in MRI	2.64	.006

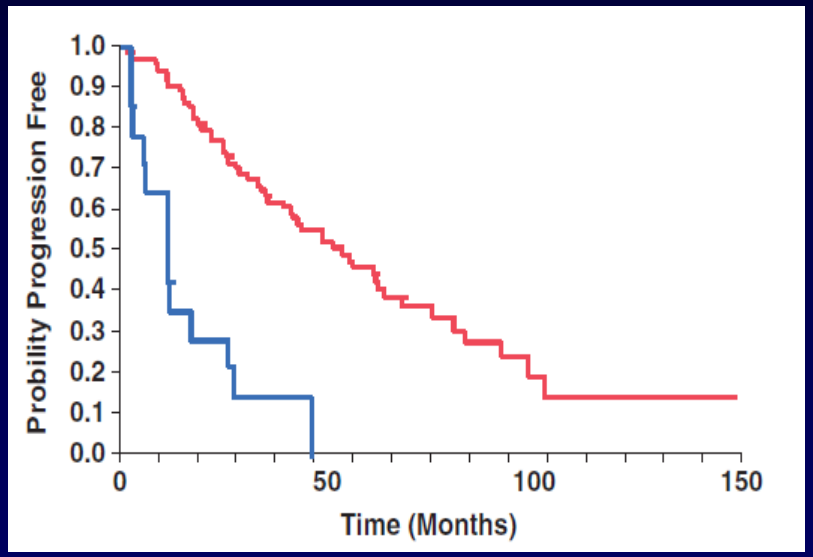
Hillengass, JCO, 2010

PET/CT

- The Bologna group (n=73)
  - Six out of 9 patients with a positive PET/CT progressed to symptomatic myeloma during their follow-up. The probability of progression within 3 years for patients with positive PET/CT was 65% vs 42% for PET/CT negative patients

- The Mayo Clinic (n=132)
  - 19/33 patients (56%) with a positive PET-CT progressed to active myeloma within 2 years; in contrast to 28% with a negative PET/CT (22)

Circulating plasmocytes



More than 5% of plasmocytes based on a immunofluorescent assay performed on fixed peripheral blood mononucleated cells.

Bianchi, Leukemia 2013

IMWG considers that a prognostic factors that is able to identify

SMM cases with ~80% risk of progression at 2 years (median time of transformation 12 months)

justifies an early intervention

Risk group	Probability of progression to myeloma or related disorder in first 2 years from initial diagnosis of SMM (%)
Bone marrow clonal plasma cells ≥60%	90
Serum involved/uninvolved free light chain ratio ≥100	80
Abnormalities on MRI (>1 focal lesion)	70
Abnormal plasma cell immunophenotype ≥95%	50
Evolving type of SMM*	65
t(4;14) or del 17p	50
M protein ≥30 g/l and bone marrow clonal plasma cells ≥10%	50
Serum involved/uninvolved free light chain ratio ≥8 and <100	40
No high-risk factors	10–20

Lancet Oncol 2014; 15: e538–48

Review

International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma

S Vincent Rajkumar, Meletios A Dimopoulos, Antonio Palumbo, Joan Blade, Giampaolo Merlini, María-Victoria Mateos, Shaji Kumar, Jens Hillengass, Efstathios Kastritis, Paul Richardson, Ola Landgren, Bruno Paiva, Angela Dispenzieri, Brendan Weiss, Xavier LeLeu, Sonja Zweegman, Sagar Lonial, Laura Rosinol, Elena Zamagni, Sundar Jagannath, Orhan Sezer, Sigurdur Y Kristinsson, Jo Caers, Saad Z Usmani, Juan José Lahuerta, Hans Erik Johnsen, Meral Beksac, Michele Cavo, Hartmut Goldschmidt, Evangelos Terpos, Robert A Kyle, Kenneth C Anderson, Brian G M Durie, Jesus F San Miguel

Diagnosis of MM requires the presence of a clonal bone marrow plasmocytosis ≥10% or biopsy proven plasmacytoma and 1 or more of the following criteria

- **Evidence of end organ damage, attributable to the underlying plasma cell proliferative disorder**
  - Hypercalcemia
  - Renal insufficiency
  - Anemia
  - Bone lesions
- **Biomarkers of malignancy**
  - Clonal bone marrow plasma cells ≥60%
  - Involved/uninvolved serum free light chain ratio ≥100
  - >1 focal lesions on magnetic resonance imaging studies

Rajkumar, Lancet Oncology, 2014

Should we treat SMM ?

Conventional chemotherapy

Agents	N	ORR (%)	TTP	OS (mo)
Early MP vs deferred MP	25 25	52 55		
MP vs observation			-	54 58
	75 70	40 55	79 48	60 71

No differences in survival and potential risk of secondary leukemia

HJjorth, Eur J Haematol. 1993
Grignani, Br J Cancer 1996
Riccardi, Br J Cancer, 2000

Should we treat SMM ?

Biphosphonates

Agents	N	ORR (%)	TTP	OS (
Pamidronate	12			-
Pamidron		-	46 48	-
nate vs Observation	81 82	-	67 59	-

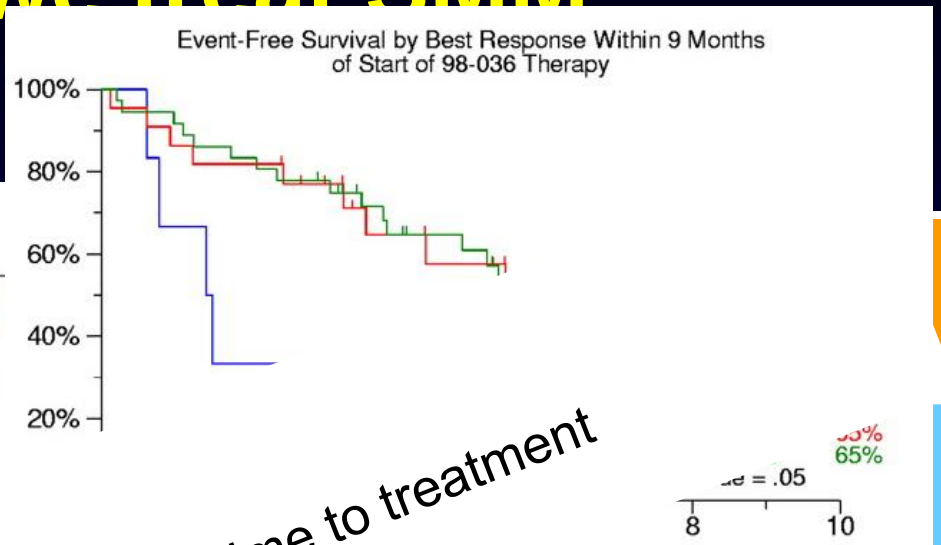
Increase of bone density and decreased bone resorption markers
SRE lower in the biphosphonates groups (39 vs 73%; 55 vs 78%)
No anti-tumor effect

Martin, Br J Haematol, 2002
D'arena, Leuk Lymphoma, 2011
Musto, Cancer, 2008

Should we treat SMM ?

Thalid

Adverse Event	*Thal/ZLD*
Any grade 2 +	32 (91%)
Any grade 3 +	17 (49%)
Any grade 4 +	5 (14%)
Any hematologic grade 3 +	6 (17%)
Any hematologic grade 4 +	1 (3%)
Any non-hematologic grade 3 +	
Any non-hematolo… grade 4 +	



~ 30% ≥ PR; high toxicity; patients achieving PR had a shorter time to treatment

			60% at 4y	91% at 4y
	35	37%	2.4 y	74% at 5y
	33	0%	1.2 y	73% at 5y

Rajkumar, Leukemia, 2003
Barlogie, Blood, 2008
Witzig, Leukemia, 2013

Should we treat SMM ?

PETHEMA trial

Selection of high risk patients

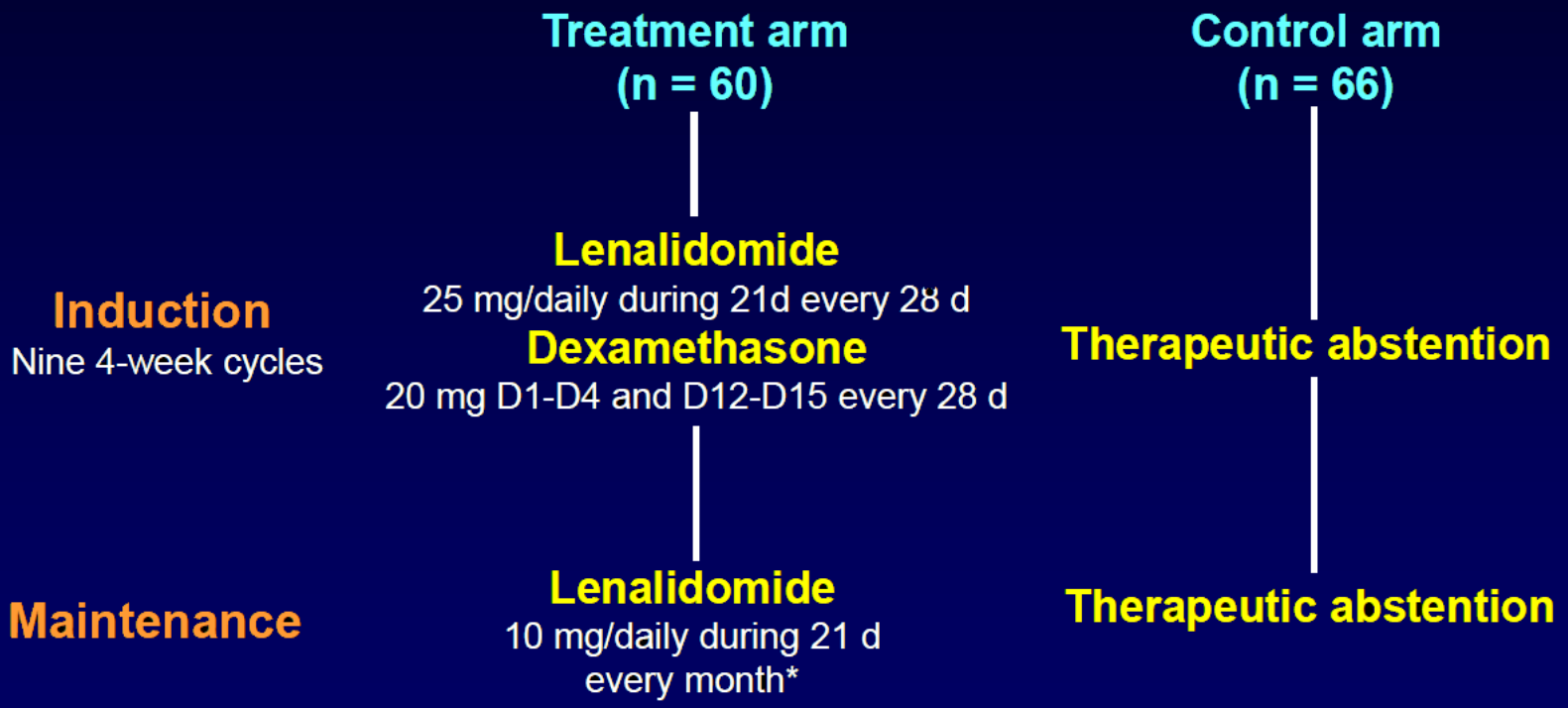
PCs BM ≥ 10% plus M-protein ≥ 30 g/L

or

BM aPC/nPC > 95% plus i**mmunoparesis**

Should we treat SMM ?

Lenalidomide

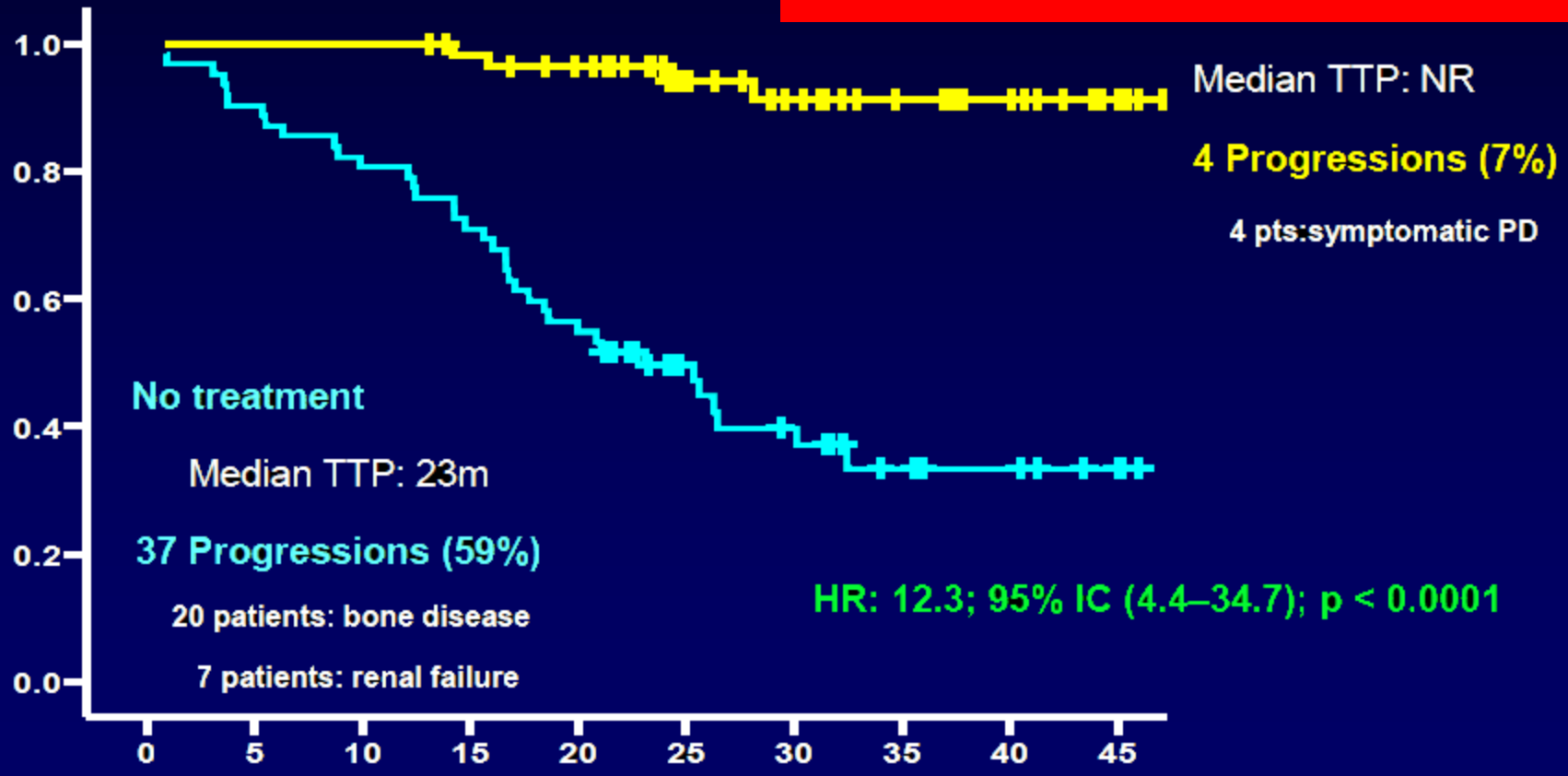


Mateos, ASH 2011

TTP to acti

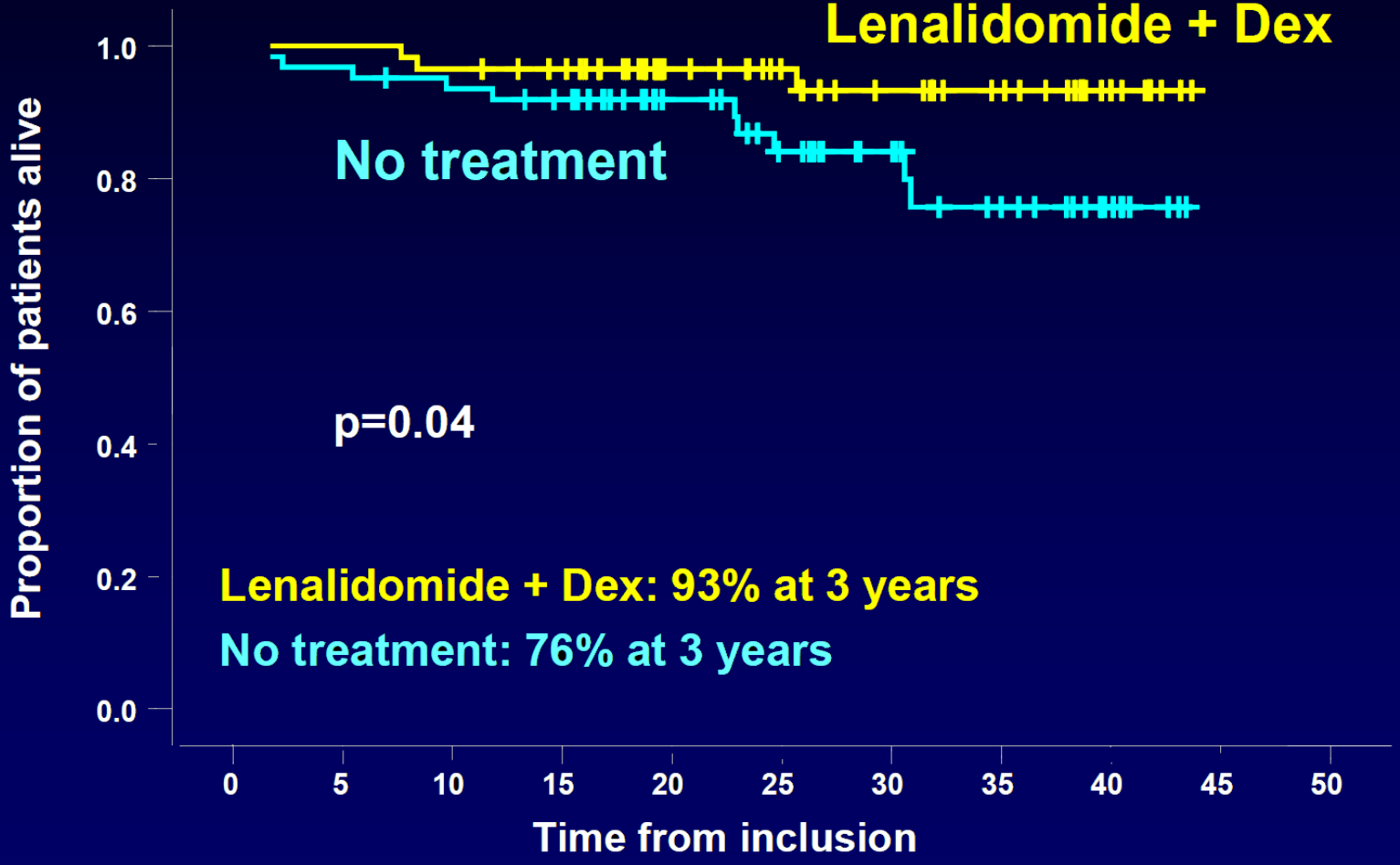
Lenalidomide maintenance
24 patients biological progressions
18 patients -- Dexa 20 mg d1-d4
3 PR
11 SD
4 MM

Median follow-up



OS from inclusion

Median follow-up: 32 months (range 12–49)



Mateos, ASH 2011

IMWG recommendations

- Ultra-risk patients are recommended to be treated
  - Potential harmful organ complications with significant long-term morbidity need to be avoided
  - Based patients' health status and patients'choice
- High risk patients should be followed regularly and might be candidates for early intervention clinical studies.
- Low risk patients: follow-up.

Conclusions

- MGUS and sMM are the most prevalent premalignant conditions in worldwide population
- Active myeloma for nearly all patients is preceded by MGUS/sMM.
- Prognostic categorization of MGUS and sMM is crucial to tailor their follow-up